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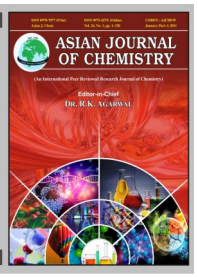

Synthesis of 3,7-Dihydroxy-3,7-dioxopenhydro-1,5,3,7-diazadiphosphocines with Various Amines

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As a part of a research program related to the synthetic study of pharmacologically interesting compounds and good chelating agent for transition metal ion, we here report the synthesis of an unusual medium-sized ring heterocyclic ligand with mixed carboxylic-amino-phosphonic donating groups. We have synthesized 1,5-diphenyl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4a**), 1,5-di(2-ethaneamine)yl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4b**), 1,5-dibenzoic acid-yl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4c**), 1,5-difurfuryl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4d**), 1,5-di[thiophene-2ylmethyl]-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4e**), 1,5-di[thiophene-2yl]-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4f**), 1,5-dipyridin-4-yl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4g**), 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (**4h**), 2-[5-(1,2-dicarboxyethyl-3,7-dihydroxy-3,7,dioxo-315.715-[1,5,3,7]diazadiphosphocan-1-yl]-succinic acid (**4i**) and 3,7-Dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (**4j**).

Keywords: 1,5,3,7-Diazadiphosphocine, Chelating agent, Magnetic resonance imaging, Amines.

INTRODUCTION

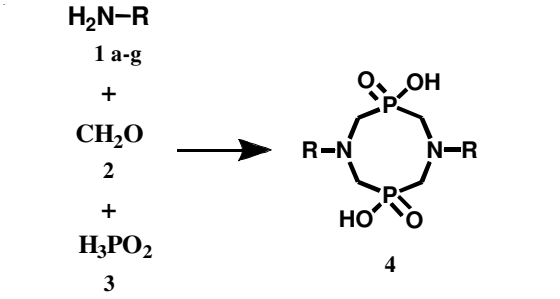
In the last few years, great efforts have been devoted to the development of efficient ligands for transition metal ions, in order to obtain complexes whose stability, physical properties and biodistribution could make them suitable for application as contrast agents for magnetic resonance imaging (MRI)[1], diagnostic-therapeutic radiopharmaceuticals[2] or fluorecent bioassay.[3]

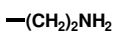
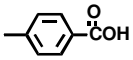
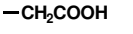
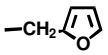
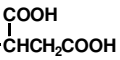
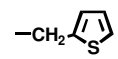
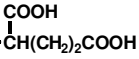
Most of these ligands belong to the huge class of poly-aminopolycarboxylic acids as diethylenetriamine-pentaacetic acid (DTPA), 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid(DOTA) and the great array of their substituted or modified derivatives[4-6]. But there is still a great effort in synthesizing new products with improved properties and for specific applications. An urgent and specific medical need is represented by the imaging of the cardiovascular system[7,8]. To perform a magnetic resonance angiography (MRA) the administered contrast agent must stay in the blood stream for a long time and three main differents ptrategies have been proposed. It is important to synthesize new bioactive compounds and contrast agents. To the best of our knowledge, there are few reports involving the reaction of hypophosphorous (wheady) acid with formaldehyde and aromatic amines. We already reported the synthesis of 1,5,3,7-diazadiphosphocine-1,5-dicarboxylic acid and their esterifications[9].

As a part of a research program related to the synthetic study of pharmacologically interesting compounds and good chelating agent for transition metal ion, we here report the synthesis of an unusual medium-sized ring heterocyclic ligand with mixed carboxylic-amino-phosphonic donating groups.

EXPERIMENTAL

Melting points were determined on an electrothermal capillary melting point apparatus and uncorected. TLC was performed on glass plates coated with silicon oxide (silica-gel 60 F_{254}) and compounds were visualized using a UV lamp. ^{1}H and ^{13}C NMR spectra were obtained with bruker AC2000 (200 MHz) and varian Gemini (200 or 300 MHz) spectrometers. Mass spectra were measured with HP 5890 GC/MASS (70 eV, EI). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use. Except where noted, all starting amterials were purchased from Aldrich, Fluka, Fisher, Lancaster or TCI Chemical Companies and used as received. The following known compounds were prepared by literature procedures[11]: ethanol, DMSO, hexane, chloroform, water, butanol, propanol,



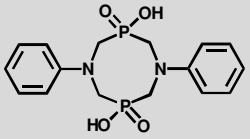
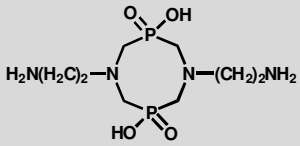
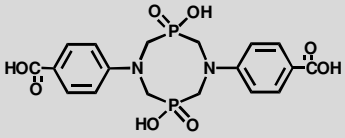
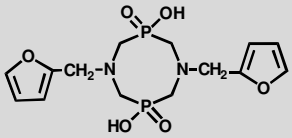
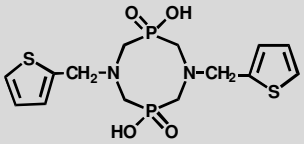
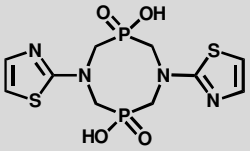
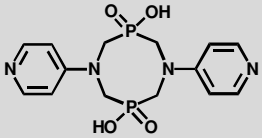
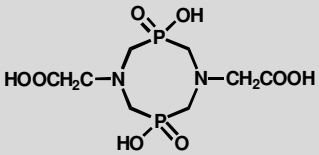
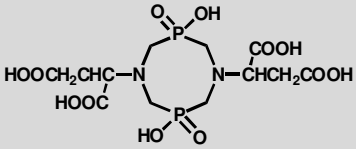
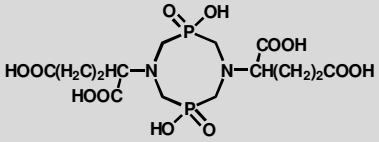
	R		
4a		4f	
b		g	
c		h	
d		i	
e		j	

and methanol. Known compounds prepared by modified procedures have been included in the supplemental information.

General procedure for the preparation of 4a-g: A mixture of aniline (0.93 g, 0.01 mol), hypophosphorous acid (0.55 mL, 0.01 mol), paraformaldehyde (1.8 g, 0.02 mol) and 6M HCl (10 mL) was stirred for 0.5 h. And then the clear solution was left standing for 3 days. The physical data of all the synthesized compounds **4a-g** are given in Table-1.

A brown solid product (9.6 %) **4a**, was then collected by filteration, washed with a small amount of cold water, ethanol and dried *in vacuo*. Unreacted starting materials remained in solation. 1,5-Diphenyl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4a**), m.p 273-274 °C; IR (KBr, ν_{max}, cm^{-1}): 3011, 1321, 1100; ^{1}H NMR (D_2O, pH 10, 200 MHz) δ: 3.17-3.21 (d, 8H), 7.18-7.35 (m, 10H); ^{13}C NMR (D_2O, pH 10, 300 MHz) δ: 53.2, 130.8, 131.9, 142.1, 148.5; MS (MOLDI-TOP), *m/z* 336 (Anal. calcd. (%) for C, 52.46; H, 5.50; N, 7.65; P, 16.91 found; C, 52.82; H, 5.36; N, 7.57; P, 16.69). 1,5-Di(2-ethaneamine)yl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4b**), m.p.: sticky oil; IR (KBr, ν_{max}, cm^{-1}): 3421, 3055, 1378, 1180; ^{1}H NMR (D_2O, pH 10, 200 MHz) δ: 3.09 (s, 8H), 3.31-3.39 (t, 4H), 3.51-3.59 (t, 4H); ^{13}C NMR (D_2O, pH 10, 300 MHz) δ: 47.3, 48.1, 58.7; MS (MOLDI-TOP), *m/z* 300 (Anal. calcd. (%) for C, 32.00; H, 7.39; N, 18.66; P, 20.63 found; C, 32.32; H, 7.46; N, 18.51; P, 20.87) 1,5-dibenzoicacid-yl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphos-phocine (**4c**); m.p.: 232-233 °C; IR (KBr, ν_{max}, cm^{-1}): 3454, 3010, 2699, 1378; ^{1}H NMR (D_2O, pH 10, 200 MHz) δ: 3.28 (s, 8H), 7.13-7.46 (m, 8H); ^{13}C NMR (D_2O, pH 10, 300 MHz) δ: 59.8, 124.3, 128.7, 132.4, 157.4, 179.8; MS (MOLDI-TOP), *m/z* 454 (Anal. calcd. (%) for C, 47.59; H, 4.44; N, 6.17; P, 13.64 found (%): C, 46.98; H, 4.67; N, 6.29; P, 13.65) 1,5-difurfuryl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4d**); m.p.: sticky oil; IR (KBr, ν_{max}, cm^{-1}): 3027, 2646, 1547, 1324, 1151, 1001; ^{1}H NMR (D_2O, pH 10, 200 MHz) δ: 3.59-3.78 (m, 8H), 5.55-5.61 (d, 4H), 7.20-8.28 (m, 6H); ^{13}C NMR (D_2O, pH 10, 300 MHz) δ: 59.8, 124.3, 132.4, 157.4, 179.8; MS (MOLDI-TOP), *m/z* 374 (Anal. calcd. (%) for C, 44.93; H, 5.39; N, 7.48; P, 16.55 found : C, 45.12; H, 5.31; N, 7.59; P, 17.00) 1,5-di[thiophene-2ylmethyl]-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4e**); m.p.: sticky oil; IR (KBr, ν_{max}, cm^{-1}): 3015, 2847, 2657, 1586, 1486, 1323; ^{1}H NMR (D_2O, pH, 200 MHz) δ: 3.70-3.73 (d, 8H), 5.60-5.65 (m, 4H), 6.92-8.37 (m, 6H); ^{13}C NMR (D_2O, pH 10, 300 MHz) δ: 59.7, 63.4, 123.7, 138.9, 142.1, 157.0; MS (MOLDI-TOP), *m/z* 406 (Anal. calcd. (%) for C, 41.38; H, 4.69; N, 6.89; P, 15.24; S, 15.78 Found : C, 41.36; H, 4.88; N, 6.99; P, 15.12; s, 15.65). 1,5-di[thiophene-2yl]-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4f**); m.p.: sticky oil; IR (ν_{max}, KBr, cm^{-1}): 3013, 2646, 1524, 1423, 1311, 1245; ^{1}H NMR (D_2O, pH 10, 200 MHz) δ 3.17-3.18 (d, 8H), 7.06-7.56 (m, 4H); ^{13}C NMR (D_2O, 300 MHz) δ 62.7, 101.3, 131.1, 162.9; MS (MOLDI-TOP), *m/z* 380 (Anal. calcd. (%) for C, 31.58; H, 3.71; N, 14.73; P, 16.29; S, 16.86 Found : C, 31.49; H, 3.80; N, 14.81; P, 16.22; S, 16.93). 1,5-dipyridin-4-yl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4g**); m.p.: sticky oil; IR (KBr, ν_{max}, cm^{-1}): 3077, 3017, 2612, 1674, 1507, 1311; ^{1}H NMR (D_2O, pH 10, 200 MHz) δ: 3.78-3.80 (m, 8H), 6.80-8.19 (m, 8H); ^{13}C NMR (D_2O, pH, 300 MHz) δ: 61.7, 108.6, 157.6, 161.4; MS (MOLDI-TOP), *m/z* 368 (Anal. calcd. (%) for C, 45.66; H, 4.93; N, 15.21; P, 16.82 Found : C, 45.62; H, 5.01; N, 15.25; P, 16.63). 3,7-Dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (**4h**): A mixture of glycine (0.75 g, 0.01 mol), hypophosphorous acid (0.55 mL, 0.01 mol), paraformaldehyde (1.8 g, 0.02 mol) and 6 M HCl (10 mL) was stirred for 0.5 h and then the clear solution was left standing 3 days. A white solid product (0.26 g, yield 8 %), was then collected by filteration, washed with a small amount of cold water, ethanol and dried *in vacuo*. Unreacted starting materials remained in solution.: m.p. 273-275 °C; IR (KBr, ν_{max}, cm^{-1}): 3445 (OH), 2999,1718 (C=O), 1652; ^{1}H NMR (D_2O, PH 10, 200 MHz) δ: 3.87(s, 4H), 3.50 (d, J = 9.3 Hz, 8H); ^{13}C NMR (D_2O), pH 10, 50 MHz) δ: 178.5, 59.2, 55.6; MS (MOLDI-TOF), *m/z* 331 (Anal. calcd. for C, 26.24; H, 5.50; N,7.65; P, 16.92 Found; C, 26.50; H, 5.53; N, 7.36; P,16.71). 2-[5-(1,2-Dicarboxyethyl-3,7-dihydroxy-3,7,dioxo-315.715-[1,5,3,7]-diazadiphosphocan-1-yl]-succinic acid (**4i**): A mixture of L-aspartic acid (1.33 g, 0.01 mol), hypophosphorous acid (0.55 mL, 0.01 mol), paraformaldehyde (1.8 g, 0.02 mol) and 6 M HCl (10 mL) was stirred for 0.5 h. And then the clear solution was left standing 3 days. And then mixture was added ether, another separated with H_2O, dried *in vacuo*. A white solid product (0.17 g, yield 7.8 %) was then collected: m.p. 238-240 °C; IR (KBr, ν_{max}, cm^{-1}) 3445 (OH), 2999, 1718 (C=O), 1652; ^{1}H NMR (D_2O, pH 10, 200 MHz) δ: 4.24 (t, J = 6.9 MHz, 2H), 3.48 (d, J = 9.2 MHz, 8H), 3.34 (m, 4H); ^{13}C NMR (D_2O, pH 10, 50 MHz) δ: 174.1, 173.4, 52.1, 50.8, 48.5. 3,7-Dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (**4j**): A mixture of L-glutamic acid (1.47 g, 0.01 mol), hypophosphorous acid (0.55 mL, 0.01 mol), paraformaldehyde (1.8 g, 0.02 mol) and 6 M HCl

TABLE-1
PHYSICAL DATA OF PRODUCTS **4a-j**

Entry	Product		m.p. (°C)	Yield[a] (%)
1		**4a**	273-274	*9.6*
2		**4b**	-	7.4
3		**4c**	232-233	5.2
4		**4d**	-	5.6
5		**4e**	-	6.1
6		**4f**	-	6.8
7		**4g**	-	8.7
8		**4h**	273-274	8.0
9		**4i**	150-152	7.8
10		**4j**	304-305	6.8

[a]Isolated yield

(20 mL) was stirred for 0.5 h. And then the clear solution was left standing 3 days. In order to precipitate solid, the clear solution in refrigerator was kept for 24 h. After filtering precipitated solid, it was washed by hexane and chloroform. A white solid product (0.32 g, yield 6.8 %) was then collected: m.p. 304-306 °C; IR (KBr, ν_{max}, cm^{-1}) 3448 (OH), 2956, 1731 (C=O), 1655; ^{1}H NMR (D_2O, pH 10, 200 MHz) δ: 4.27 (s, 2H) 3.50 (d, *J* = 9.3 Hz, 8H), 2.42 (t, *J* = 6.9 Hz, 4H), 2.08 (m. 4H); ^{13}C NMR (D_2O, pH 10, 50 MHz) δ: 173.0, 172.6, 170.4, 169.7, 52.3, 51.5, 48.9, 25.8.

RESULTS AND DISCUSSION

As a part of research program related to the synthetic study of pharmacologically interesting compounds and good chelating agents for transition metal ions, we here report the synthesis of an unusual medium signed ring heterocyclic ligand with mixed aminophosphonic donating group. In order to synthesize 1,5-di(2-ethaneamine)-yl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4a**), 1,5-di(2-ethaneamine)-yl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4b**), 1,5-dibenzoicacid-4-yl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4c**), 1,5-difurfuryl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4d**), 1,5-di[thiophene-2-ylmethyl]-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4e**), 1,5-di[thiazol-2-yl]-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4f**), 1,5-dipyridin-4-yl-3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine (**4g**), 3,7-dihydroxy-3,7-dioxo-perhydro-1,5,3,7-diazadi-phosphocine-1,5-diaceticacid (**4h**), 2-[5-(1,2-dicarboxyethyl)-3,7-dihydroxy-3,7-dioxo-3[1,5,3,7]-diazadiphosphocan-1-yl]-succinic acid (**4i**), and 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (**4j**). These reactions were then performed, adopting various aromatic groups and aminoethyl group with glycine in aq. HCl.

The strongly acidic medium is required to promote the second reaction of H_3PO_2 and to avoid the side reactions of the iminium ion such as the reduction by means of formaldehyde to N-methyl derivatives. The reaction was found to be highly dependent on the experimental conditions employed. High concentrations of the reactant, heat and very long reaction times led to extensive formation of polymeric products; conversely, low acidity (pH > 1) and low reactant concentrations gave rise to complex mixtures. A clean reaction was effected dissolving glycine and H_3PO_2 in 6 M HCl to obtain a 1.0 M solution in both reagents and adding paraformaldehyde in slight excess (3 equiv.) in one portion. Complete dissolution was achieved by stirring for 3 days. A white solid product was then collected by filtration, washed with a small amount of cold water, ethanol and dried *in vacuo*. NMR analysis of the product showed a highly symmetrical molecule, (two signals in ^{1}H NMR and three signals in the ^{13}C NMR) with a molecular weight of 330 a.m.u. characterized as 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (**4h**). This heterocyclic ligand results from the assembly of two molecules of glycine, two molecules of H_3PO_2 and four molecules of formaldhyde; its striking feature is that each atom of this eight-membered ring is originated from eight single different molecules, representing a formal '1+1+1+1+ 1+1+1+1' cyclocondensation. The yield is satisfactory despite the number of elemental steps involved in the overall transformation and of the ring size, usually unfavorable for entropic reasons. In case of aspartic acid with paraformaldehyde and H_3PO_2 we could obtain 2-[5-(1,2-dicarboxyethyl)-3,7-dihydroxy-3,7-dioxo-315.715-[1,5,3,7]diazadiphosphocan-1-yl]-succinic acid (**4i**). Work-up step to get **4i** is very different and difficult than those of **4h** and **4j**. We remarked work-up step to get **4i** at the experimental section. The reaction of glutamic acid with paraformaldehyde and H_3PO_2 gave 3,7-dihydroxy-3,7-dioxo-perhydro-1,5,3,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (**4j**).

The relative position of the functional groups is particulary interesting in view of the possible application of carboxylic acid (**4h**) as ligand for metal ions. The N-CH_2COOH and N-CH_2-P(O)OH-CH_2-N moieties are known to chelate efficiently through formation of five-membered rings with the metal atom. Furthermore, the latter is embraced by the six donor atoms in a nearly ideal octahedral arrangement, highly advantageous for the complexation of the hexacoordinated transition metal ions. Hence we will start a preliminary investigation on the binding properties of carboxylic acid (**4h**) towards Mn^{2+} and Gd^{3+}, two paramagnetic ions of choice in the design of contrast agents for MRI, with different chemical behaviors and whose magnetic features help in the investigation of the solution structures of the corresponding adducts.

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